

STAT

Page Denied

STAT

DATA ON AND TASKS OF STUDY OF ANTIBIOTICS IN USSR

[Comment: The following report on current trends in the field of antibiotics by Z. V. Yermol'yeva appeared in the bimonthly Moscow periodical Antibiotiki, Vol 1, No 1, January/February 1956. under the title "New Data and Basic Tasks in the Study of Antibiotics."]

The discovery of antibiotics marks the beginning of a new era in medicine. Antibiotics are of the greatest significance not only for medicine but also for veterinary practice and for agriculture. They form the subject of many-sided studies within the scope of various biological and chemical disciplines.

The sources from which antibiotics are obtained vary. About 100 antibiotics have been isolated from bacteria, although only tryothricin, gramicidin S, bacitracin, and polymixin have found application in medicine.

Actinomycetes proved to be a very prolific source of antibiotics. Antibiotics derived from actinomycetes are effective in the therapy of many diseases of human beings, animals, and plants. The substances in question are also used as growth stimulants and as preservatives of biological preparations. Mycetin, globi-porin (Krasil'nikov), albomycin (Canze et al), and grisemin (Planel'es) have been isolated from actinomycetes in the USSR.

Streptomycin, as is well known, is used extensively in the therapy of many infections brought about by gram-positive and gram-negative bacteria. Specifically, streptomycin remains one of the principal agents for the therapy of various forms of tuberculosis and plague. Levomycetin (chloromycetin), biomycin (aeromycin), terramycin, tetracycline, and erythromycin are effective in the treatment of various bacterial and rickettsial infections as well as in some virus diseases. Streptomycin, grisemin, and actidione have found application in the therapy of various plant diseases. One must regard as promising the therapy of fungi infections with thiolutin, nistatin (Tasen, Sloane), and candidin.

The discovery abroad of azaserin, sarcomycin, and puromycin gives rise to hope that antibiotic agents will be isolated which may prove active against malignant neoplasms.

Very promising is the isolation of antibiotics from animal tissues. A few examples of antibiotics of this type are lysozyme (Ishchenkov, Fleming), erythrin (Zil'ber, Yakobson), and ekmolin (Yermol'yeva). It is of importance that ekmolin proved active against the virus of influenza of the A type. Recently, the antibiotic properdin has been isolated from blood serum by Pillemer. Properdin proved to be effective in alleviating complications produced by radiation sickness.

A number of investigations dealt with the action of antibiotics on macroorganisms and microorganisms.

Notwithstanding the fact that the decisive influence on the outcome of therapeutic treatment is exerted by the state of the macroorganism, the specific action of the antibiotic on the causative factor of the infection is an exceptionally important stage of antibiotic therapy. Pathogenic microorganisms which are under the influence of antibiotics and are brought into a depressed state as a result of this succumb more readily to the action of the protective forces of the organism, so that final recovery is assured.

STAT

Antibiotics are specific as far as their action is concerned, because they exert a selective effect on the metabolic processes of definite microorganisms. One may regard as established that penicillin interferes with the metabolism of amino acids and streptomycin with the oxidation of carbohydrates, while levomycetin suppresses the hydrolysis of fats and biomycetin the synthesis of proteins. Moreover, it could be established that under the action of aureomycin, the synthesis of adaptive enzymes is suppressed and that formation of volatile phenols from tyrosine takes place in the intestine (Schorm, Gruenberger, Skoda).

Microorganisms which are sensitive to antibiotics differ from those which are insensitive as far as their composition is concerned. Staphylococci which are sensitive to penicillin lack lysine while those which are resistant to penicillin do not contain glutamine or ornithine. When the resistance of *B. coli* to chloromycetin is enhanced, the level of aspartic acid diaminase is reduced. In work conducted with the aid of tracer atoms it was established that penicillin combines irreversibly with microorganisms that are sensitive to it.

Less thoroughly investigated is the mechanism of the action of antibiotics on the macroorganism. This action may be physiological in addition to being toxicallergic. The significance of the physiological state of the higher divisions of the cerebrum for the success of antibiotic therapy has been demonstrated (Yudintsev, Chernukh).

It has been shown in V. N. Chernigovskiy's laboratory that in addition to exerting an antimicrobial action, streptomycin eliminates some reflex mechanisms which keep the pathological process going (Kan).

The effect of penicillin on the proliferation of connective tissue at the focus of infectious inflammation has been experimentally proven (Chernukh, Timofeyevskaya). According to I. A. Kassirskiy's data, phagocytosis and the complement titer are increased under the effect of penicillin combined with ekmolin. It has been established at our laboratory that joint administration of penicillin and ekmolin is capable of activating the elements of the reticulo-endothelial system.

A. P. Avtsyn established that antibiotics not only lower the degree of intoxication, but are also capable of changing radically the morphological substrate of infectious diseases. When the therapy is fully effective, antibiotics contribute to rapid remission of morphological modifications with the exception of extensive destructive and scar processes.

One must constantly keep in mind that as a result of the systematic application of antibiotics, the classical forms of infection are changed and thus a new pathology of infectious diseases is produced as a result of therapy with antibiotics (Planel's, Rudnev, Avtsyn).

Of great importance for the success of antibiotic therapy are the condition of the macroorganism, the form which the pathological process assumes, and the stage of the disease. It is also known that an important role is played by the sensitivity of microorganisms to the antibiotic, the concentration of the antibiotic at the focus of the infection, and the correct selection of the medicinal form. The chances of successful therapy are lowered as a result of the formation of resistant forms of microorganisms under the influence of antibiotics.

At the same time, one may with the aid of antibiotics readily obtain nonvirulent forms of microorganisms, i. e., of spirochetes, staphylococci, and anaerobes (Yermol'yeva, Sherishorina). The microorganisms are changed to such an extent that some investigators consider it possible to use this method for the development of new species (Moroz).

STAT

The application of antibiotics to obtain bacteria that have been changed in a desired sense, so that live vaccines can be prepared from them, is entirely logical.

Most effective in the control of infectious diseases brought about by resistant forms of microorganisms is the combined therapy by applying a number of different antibiotics which have different chemotherapeutic characteristics. Additional application of hormone preparations and vitamins is also effective. Some workers, in order to avoid the formation of resistant forms of microorganisms, recommend that penicillin be applied only parenterally while bacitracin, polymixin, and neomycin are applied locally.

It has been proven that streptomycin and penicillin always exert a synergistic effect. This particular combination can be used to advantage in infectious diseases other than syphilis. According to clinical data obtained at Kassirskiy's clinic, streptomycin and penicillin produce a good synergistic effect in combination with ekmolin. Combining penicillin with ekmolin prevents the appearance of resistant forms of pneumococci, as has been shown in the treatment of pneumonia of children (Dub).

However, one cannot always combine any antibiotics with any other antibiotics. It has been established at our laboratory that in experimental staphylococcus infections penicillin and biomycin act as antagonists. The effect produced by this combination is the same in experimental diphtheria infections (Iskrzhitskaya). According to data reported by foreign authors, an antagonism between penicillin and aureomycin is observed in the therapy of experimental psittacosis, and one between penicillin and chloramphenicol in pneumonia and salmonellosis. An adverse effect as a result of combining penicillin with aureomycin has also been observed in the therapy of pneumococcal meningitis (Lerner). In such cases the antibiotics must be administered in succession and not combined with each other.

In a number of infections (brucellosis, dysentery, typhoid) it is advisable to combine administration of antibiotics with that of vaccines, because, according to some data, an early application of antibiotics in large doses may impair the development of immunity.

The problem of the side effect of antibiotics should not be lost sight of. Among side reactions which occur in connection with antibiotic therapy, one ought to mention secondary infections and allergic reactions as well as toxic reactions which are connected with the action of the antibiotic itself or with the rapid liberation of bacterial toxins when shock doses are given.

Superinfections are connected with the inhibition of sensitive microbes and acceleration of the propagation of a resistant flora when antibiotics of a broad spectrum of activity (synthomycin, streptomycin, or tetracycline) are used. The prevalence in the intestine of pathogenic staphylococci and yeast fungi sometimes brings about colitis, enterocolitis, or a general infection referred to as candidomycosis. Usually these conditions are connected with a lowering of the resistance of the patient. Kashkin and Arievidh described several cases of candidomycosis which led to the death of the patients. Particularly acute is pseudomembranous enterocolitis brought about by staphylococci and occurring after administration of tetracyclines. This complication can be successfully treated by administration of erythromycin. In order to control disbacteriosis and candidomycosis, it is advisable to apply antibiotic preparations combined with *B. coli* or with the antifungal substances candidin and nistatin. It is also expedient to prescribe sodium caprylate, methylparaben, and propylparaben, substances which suppress fungi infections. Changes which take place in the oral cavity during the treatment with antibiotics may be a consequence of avitaminosis due to the lack of vitamins of the B group.

STAT

For that reason, patients afflicted in this manner are treated with vitamin B complex or riboflavin. However, the normal flora is rapidly restored after treatment has been discontinued. According to the data obtained at the Chair of Microbiology of the Central Institute of Advanced Training for Physicians, no harmful consequences take place as a result of the changes in the microflora.

At present, descriptions of the following allergic reactions occurring after administration of antibiotics have been given: dermatitis of various degrees of severity, rash, itching, vasomotor rhinitis, sometimes pain in the joints, swollen lips and eyelids, and eosinophilia. When the application of the antibiotic is carried out by the aerosol method, symptoms of this type develop in a greater number of persons (up to 5%). To prevent the symptoms, one should use penicillin of the O type, dimedrol, adrenalin, calcium chloride, or euphyllin. To bring about desensitization, it is advisable to administer the antibiotics beginning with very small doses.

It is also advisable to carry out skin tests in order to determine the degree of sensitivity to penicillin or streptomycin.

When penicillin is applied locally to the brain, its action is toxic. For that reason, it should be administered endolumbarly with particular precautions. The toxic action of streptomycin on the auditory nerve and of biomycin on the digestive system are well known.

Synthomycin and levomycetin are capable of suppressing the activity of the bone marrow as far as blood formation is concerned. Some authors have described leukopenia and aplastic anemia that arise as a result of the administration of these antibiotics. For this reason, constant watch must be kept over the composition of the blood when therapy with these antibiotics is applied.

Prolonged application of large doses of biomycin, terramycin, and tetracycline may bring about a fattening of liver cells. To reduce the side effects produced by biomycin, this antibiotic should be combined with ekmolin or applied in fractional doses. G. P. Rudnev proposes that antibiotics be administered by the interrupted cycle method.

The control of the side effects produced by antibiotics can be accomplished by developing new medicinal forms, preparation of derivatives of antibiotics which have a prolonged action and are convenient in application, or finally the development of preparations which are accumulated selectively in definite organs and exhibit a wider spectrum of activity by reason of a partial modification of their chemical constitution.

Penicillin is now being supplied only in the crystalline state. The medical industry produces novocain salts of penicillin which have a prolonged action in the form of novocillin and ekmonovocillin, preparations that have been developed at our laboratory. Ekmonovocillin has the capacity of acting on resistant forms of microorganisms. After a single administration it is retained in the organism for a period of up to 36 hours. This preparation is also effective in postinfluenza encephalitis and pneumonias, according to data obtained at clinics directed by N. I. Grashchenkov, M. S. Vovsi, I. A. Kassirskiy, V. N. Braytsev, and Ya. Yu. Shpirt.

At the present time, Lazareva has developed at our laboratory a preparation which has a still more prolonged action, i. e., bicillin (dibenzylethylenediamine-penicillin). On being administered in a dose of 300,000 units, this preparation is retained in the body for 7 days, while administration of 600,000 units results in retention up to 10 days. According to experimental data, the preparation is effective in pneumonia, sepsis, and syphilis. According to published data, one should use 1,200,000 units of bicillin once every 3 weeks in the therapy of rheumatic fever.

STAT

A number of investigators incline to the view that this preparation makes possible the prevention of rheumatic attacks. At the same time, administration of bicillin brings about only a low concentration of this antibiotic in the blood and the organs. For that reason, it is advisable to introduce it in combination with the novocain or potassium salt of penicillin. In the literature a penicillin of this type is called parpenicillin; we refer to it as bicillin 2-3. For obvious reasons, this preparation is of special value for prophylactic purposes.

It has been shown in experimental work carried out at our laboratory that if mice are infected with staphylococci, streptococci, or pneumococci even 5 days after bicillin has been administered, the majority of animals survives.

Of great value are also new preparations for peroral use. The use penicillin-histidine and penicillin-ekmolol salts, which have been developed at our laboratory, assures that a therapeutic concentration is present (in the body) for a period up to 20 hours. The novocain salt is used successfully in peroral administration together with benamide or ethamide, drugs which inhibit the elimination of penicillin by the kidneys (Vladimirov, et al.).

B. Ye Votchal proposed an effective method of applying an aerosol of dry penicillin which can be administered to advantage in the therapy of bronchitis and other diseases of the respiratory organs.

Of importance are penicillin-estopen, which contains iodine and is a preparation that accumulates mainly in the lungs, and ester-penicillin, which accumulates predominantly in the liver and in the gall bladder. Of great interest is the new preparation penicillin O, which does not produce allergic reactions. Antihistaminic properties are also exhibited by bicillin, the penicillin-histidine salt, and the penicillin-ekmolol salt, as well as by the combination of penicillin with cortisone. Of interest is the combination of penicillin with streptokinase and streptodornase, enzymes of streptococci which are capable of dissolving blood clots. The application of these combinations in surgical and therapeutic practice is particularly important.

Among new preparations developed abroad, bentamine, hydrabamine (compocillin) and the acid-resistant penicillin V for peroral administration deserve particular attention.

The therapy with streptomycin as is well known, gives rise to very large quantities of resistant forms of bacteria (i. e., of tuberculosis bacilli, staphylococci, and streptococci). For that reason, the majority of the new medicinal forms of this antibiotic have the purpose of overcoming the resistance of the bacteria in question. In addition to streptomycin-PA3, a compound of streptomycin with isoniazid also deserves attention; the latter produces a good therapeutic effect in various forms of tuberculosis. Of interest are also combinations of penicillin with streptomycin and of streptomycin with ekmonocillin. According to published data, the combination of penicillin with streptomycin is particularly effective in experimental radiation sickness.

A number of new preparations has been developed which extend considerably the spectrum of activity of penicillin and streptomycin. The preparations in question are derivatives of tetracycline. Among them is oxytetracycline (terramycin), chlorotetracycline (biomycin or aureomycin) and finally tetracycline itself.

All these preparations proved effective in pneumonias, typhoid, brucellosis, dysentery, and staphylococcal bacterial endocarditis. In many cases, when penicillin or streptomycin was inactive, the application of biomycin or terramycin yielded a positive effect. Tetracycline alleviates amebiasis, is effective in trachoma and, according to published data, yields good results in

STAT

typhoid. Biomycin exerts an effect on ascaride larva and strongyloides (Mog-hkovskiy). Unfortunately, tetracycline derivatives exert a local irritating effect upon being administered perorally and often produce nausea and vomiting.

Novocain sharply reduces the irritating effect of antibiotics of the tetracycline series. It has been found possible to introduce intramuscularly biomycin in combination with ekmolin and novocain (Yermol'yeva). When this method is used, the effective dose is smaller by a factor of 10-15 as compared with the dose for internal administration. The investigation in question was carried out by us together with G. I. Magakyan on 150 simians including 51 animals which had dysentery. Positive results were also obtained at Sukhumi hospitals in the treatment of patients suffering from dysentery, pneumonia, and sepsis (Magakyan, Papaskua).

According to data obtained by Marshak at a clinic directed by V. I. Struchkov, biomycin in combination with ekmolin and novocain, on being administered intramuscularly, yielded a pronounced therapeutic effect in the treatment of patients suffering attack from bronchiectasia. The patients bore the treatment very well: no side effects developed with the exception of a slight sensation of burning at the place of the injection. Intramuscular administration of terramycin proved to be no less effective (terracyclin was injected in a quantity of 20-30 milligrams, 2-3 times per day).

Thirty patients with suppurative processes of the lungs, some of whom were in a very serious condition prior to the treatment, responded well to intramuscular administration of terramycin together with a 2% solution of novocain. As a result of the administration of 25-30 milligrams of terramycin or biomycin, a therapeutic concentration of these antibiotics was present for 8 hours. This means that the dose of the preparations was 10-15 times smaller than that needed in peroral administration. The antitoxic function of the liver of patients who had received biomycin or terramycin intramuscularly was not affected in a single case. This testifies to the absence of a toxic effect of the preparations on the liver when the doses mentioned were administered. At a clinic directed by N. N. Yelansky administration of biomycin in combination with novocain is used extensively in the therapy of peritonitis.

We proposed a mixture of biomycin with ekmolin and sugar syrup to be used in the treatment of carriers of diphtheria bacilli and in the therapy of acute catarrhs of the upper respiratory tract and of scarlet fever. According to the opinion of clinicists, this mixture brings about the most rapid elimination of diphtheria bacilli (Sukhareva).

Antibiotics must be applied purposefully and only according to exact indications. Physicians must be aware of the fact that antibiotics can not replace surgical treatment, antitoxic sera, and sanitary and hygienic measures. In every case of medical treatment it is necessary to set a precise diagnosis of the disease and carry out bacteriological tests. It is necessary to use extensively for the determination of the sensitivity of microorganisms paper disks impregnated with antibiotics. Such disks are supplied by the USSR medical industry.

At present, antibiotics are being used extensively in medicine and also in agriculture. They are being subjected to investigation in the laboratories of various countries. However, researchers in these fields are faced by a number of problems which have not yet been solved. In order to solve these problems one must work along the following lines:

STAT

1. It is necessary to develop ways for exerting a general effect on the macroorganism in the process of antibiotic therapy, so that specific and non-specific protective reactions will be reinforced.
2. One must investigate the mechanism of the action of antibiotics and develop means of controlling the side effects produced by them.
3. One must develop more nearly perfect preparations for the control of typhoid, brucellosis, influenza, dysentery, and complications arising in experimental radiation sickness.
4. One must conduct extensive work with the aim of finding effective antibiotics which will be active against poliomyelitis, measles, rabies, and cancer.
5. One must find antibiotics which will be effective against pathogenic species of yeast, dermatophytes, and microorganisms which are pathogenic under certain conditions only.
6. One must apply more extensively antibiotics in animal husbandry and agriculture and also investigate the effectiveness of antibiotics in such applications.

* * *